REMARKS

Claims 77-148 are currently pending in the application.

Claims 72-76, 80-86, 93-129, 133-139, and 146-148 stand rejected, as explained in detail below.

Claims 77-79, 87-92, 130-132, and 140-145 have been withdrawn as being directed to non-elected species.

Claims 72, 96, and 125 are independent. Claims 72 and 125 are currently amended. Claim 96 has not been amended and is believed to patentably distinuguish over the references, as explained further below.

Claims 72-76, 80-86, 93-129, 133-139, and 146-148 stand rejected over Curatolo (US 5,605, 889), further in view of Handsfield, Urquhart (US 4,851,231), and Edgren (US 4,522,625). The Examiner stated, in pertinent part:

> Curatolo teaches a dosage form that can comprise from 25 mg to 3 grams of azithromycin (col. 4, lines 51-54). During in-vitro analysis utilizing USP-2 dissolution apparatus under the conditions of 900ml approx. 0.1M diabasic sodium phosphate buffer, pH 6.0, 37 oC, with paddles turning at 100 rpm, the azithromycin dosage form of Curatolo et al. exhibits 90% dissolution within 15 minutes when an amount of the dosage form is equivalent to 200 mg (col. 5, lines 27-35). The tablets can be film-coated with hydroxypropylmethylcellulose (col. 7, line 65-col. 8, line 2).
>
> Handsfield teaches that 2.0 grams of azithromycin treat uncomplicated gonorrhea.
>
> Urquhart teaches that certain drugs such as erthromycin should not be administered to the stomach but to the intestine over time.
>
> Edgren teaches a dispenser for releasing drug formulations, such as in the gastrointestinal tract over a prolonged period of time. The dispenser is comprised a body having a wall that surrounds an internal compartment, and can be shaped round or as a capsule. Passageways are included in the dispenser such as aperatures, orifices, bores, holes, and the like (col. 5, lines 32-43).
>
> One with ordinary skill in the art would have been motivated to use 2 grams of azithromycin in a single dose in order to obtain the beneficial effects of using such a dosage amound (see Handsfield). Whereas Curatolo does not disclose the dissolution rate of the drug at 1 hour, 2 hour, 4 hours, etc. and that the dosage form is controlled release, Curatolo does disclose the dissolution otime of a 200 mg dosage form, which corresponds to that of the instant invention. Thus, one with ordinary skill in the art would know a suitable dissolution rate for delivery azithromycin

(which corresponds to the instant invention). One with ordinary skill in the art would have been motivated to administer a form at a dissolution rate taught by Curatolo to administer the dosage form to the gastrointestine as opposed to the stomach.

Further to the above, the instant invention fails to claim the amount of azithromycin contained within the dosage form. [Office Action, pages 2-3]

The Examiner is urged to reconsider, especially in light of the claims as now amended.

The invention is directed, *inter alia*, to a controlled release dosage form of azithromycin, as defined in terms of *in vitro* test criteria. The dosage form can operate by sustained release, as claimed in claims 72 and 125, or by delayed release, as claimed in claim 96. The claims are limited to azithromycin as the antibiotic.

Applicants have now amended claims 72 and 125 to state that the dosage form releases not more than 70% of its contained azithromycin within one half hour following ingestion, as supported at page 2, lines 22-24, and line 27. It is not seen how a claim directed to a controlled release dosage form of azithromycin can be supported by Curatolo 5,505,889, the primary reference, which teaches immediate release and, accordingly, teaches away from controlled release. Curatolo claim 1 (see also claims 4 and 9) requires that the claimed dosage forms therein effect dissolution of at least 90% of their contained azithromycin within 30 minutes when tested by the method and under the conditions also disclosed therein. The claim clearly requires an azithromycin dosage form to effect immediate and/or fast release of its contained azithromycin, i.e., 90% within 30 minutes. This constitutes a requirement and/or teaching directly away from the instant dosage forms which are now expressly required to release not more than 70% of their contained azithromycin within one half hour following ingestion.

The secondary references cannot otherwise be combined with Curatolo in a way that renders the invention obvious. It is not seen how Curatolo, which teaches nothing about controlled release can be combined with secondary references that teach nothing about azithromycin. None of the secondary

references makes any suggestion to put azithromycin in a controlled release dosage form. In this respect, Edgren and Urquhart are simply examples of controlled release dosage forms, but with no suggestion to put azithromycin in a controlled release dosage form. Handsfield simply demonstrates that azithromycin is a good, effective antibiotic.

In this regard, Applicants repeat that a combination of references is improper unless the prior art suggests the combination, which is not the case here. The primary reference, Curatolo, is unrelated to controlled release and the secondary references teach nothing that would lead one of only ordinary skill in the art to modify Curatolo in such a way as to make the claimed invention obvious. See In re Bond, 15 Uspq2d 1566 (Fed. Cir. 1990) in which it was held that the PTO erred in rejecting a claimed invention as an obvious combination of the teachings of two prior art references when the prior art provided no teaching, suggestion, or incentive supporting the combination. See also Smithkline Diagnostics v. Helena Laboratories Corp., 8 USPQ2d 1468, where the court stated that a challenger to the validity of a patent "cannot pick and choose among the individual teachings of assorted prior art references to recreate the claimed invention"; the challenger has the burden to show some teaching or suggestion in the references to support their use in the particular claimed combination. In the instant rejection, the Examiner has not cited any such teaching or suggestion. See also In re Mahurkar Patent Litigation, 28 USPQ2d 1801 (N.D. Ill. 1993) where it was stated that decomposing an invention into its constituent elements, finding each element in the prior art, and then claiming it is easy to reassemble these elements into the invention is a forbidden *ex post* analysis.

> An invention lies in a combination of elements that are themselves mundane.....Unless the prior art itself suggests the particular combination, it does not show that the actual invention was obvious or anticipated. [28 USPQ2d at 1817]

To summarize, it is Applicants' position that their controlled release dosage form cannot be obvious based on a primary reference that teaches immediate release, (thereby teaching away from the invention) with secondary references that teach nothing about azithromycin. The only way one of ordinary skill would find the instant invention obvious is by an impermissible hindsight analysis, as Applicants have argued previously.

Independent claim 96 has not been amended as it is believed that it already patentably distinguishes over the references. Claim 96 requires, *inter alia*, (1) that less than 10% of azithromycin is dissolved within the first ten minutes in a first dissolution stage and (2) that less than an additional 10% (in addition to that dissolved in the first quarter hour, $Q_{0.25}$) is dissolved within a half hour ($Q_{0.5}$). Thus claim 96, as it stands, requires that less than 20% of the dosage form's contained azitrhromycin be dissolved within a half hour following ingestion. This is again to be contrasted with Curatolo which requires at least 90% dissolution within 30 minutes. The secondary references suggest nothing that would lead to a different conclusion, Applicants' arguments from above being incorporated by reference in this regard.

The Examiner's comment that the instant invention fails to claim the amount of azithromycin contained within the dosage form is noted and traversed on the basis that it should not be required. Patentability in the instant invention is not predicated on the amount of azithromycin contained in the dosage form. Further, an amount is not required to distinguish over the art. Nowhere is the amount of azithromycin characterized as being critical. Applicants dosage forms are particularly useful for higher amounts of azithromycin. See page 4, lines 18-25 in this regard. However, Applicants dosage forms reduce the incidence of side effects, even though the incidence of side effects may be lower at lower dosages.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

Date: Sept. 24, 2003

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